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EDITORIAL COMMENT

Cardiac Autonomic Imbalance in Pre-Hypertension and in a Family History of Hypertension*

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The autonomic nervous system plays a crucial role in the pathogenesis of essential arterial hypertension (1). Several studies have demonstrated that hypertensive patients have an impaired cardiac autonomic function (2). Chronic imbalance of the autonomic nervous system is a potent risk factor for adverse cardiovascular events (3). Although not widely recognized by clinicians, this risk factor is easily assessed by measures of heart rate variability during supine position, postural changes, and during deep breathing (4).

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Most studies of autonomic function in hypertension have been studied in selected groups with established hypertension and in a limited number of hypertensive offspring. However these studies were not population-based. In this issue of the *Journal*, Wu et al. (5) compared the cardiac autonomic function in 4 groups, namely normotensive subjects with and without a positive family history of arterial hypertension and pre-hypertensive and hypertensive subjects. The cardiac autonomic function was determined by SD of RR-interval, power spectrum in low frequencies (LF) and high frequencies (HF) and the LF/HF ratio in supine position for 5 min, the ratio between the longest RR-interval at approximately the 30th beat and the shortest RR-interval at approximately the 15th beat after standing (30 max/15 min ratio), and the ratio between the longest RR-interval during expiration and the shortest RR-interval during inspiration (E/I ratio). This study demonstrated that there was a decreased parasympathetic modulation of the heart in normotensive subjects with a positive family history of arterial hypertension, pre-hypertension, and arterial hypertension. Pre-hypertensive subjects manifested a significant impaired parasympathetic activity and enhanced modulation of the heart. The impairment of the cardiac parasympathetic drive existed in hypertension, but the autonomic imbalance with an augmented sympathetic shift was not significantly enhanced.

Sympatho-vagal imbalance has a major impact on blood pressure variability, which is a predictor for cardiovascular morbidity and mortality. It has been shown that sympathetic nerves do not influence variability, because no change was seen with drugs acting on either beta or alpha adrenergic receptors. No correlation was found with plasma catecholamines or sympathetic function tests. By contrast, clear inhibition was demonstrated with atropine, indicating an important role of vagal nerves on blood pressure variability (6). However, in men, inhibition was not complete with atropine; thus other mechanisms also play a role but at present are unknown.

There is limited information regarding the interaction of the autonomic balance and the renin-angiotensin-aldosterone system (RAAS). In a previous study, we examined the changes of the RR-interval and blood pressure variability with power spectral analysis during postural changes in borderline arterial hypertension and a normotensive control group (7). At the same time plasma renin activity, angiotensin II, and aldosterone were sampled. The results indicated that in borderline arterial hypertension, LF and HF of the blood pressure were already significantly increased at rest. Moreover, in borderline hypertension, renin release during postural changes correlated well with the decrease in the power of the HF vagal component of RR-interval variability and with the increase of the LF component of diastolic blood pressure variability. The TROPHY (Trial of Preventing Hypertension) study demonstrated that angiotensin II receptor blockade in pre-hypertension can prevent or postpone the development of stage 1 hypertension (8). Further studies are warranted to unravel the effect of RAAS blockade on the cardiac imbalance in pre-hypertension and its effect to prevent development of hypertension.

Atrial fibrillation and hypertension are 2 prevalent and often coexistent conditions. Several observations suggest that the autonomic nervous system plays an important role in both the initiation and/or the maintenance of atrial fibrillation. Heart rate variability analyses showed that autonomic imbalance is present before the onset of paroxysmal auricular episodes (9). The HARVEST (Hypertension and Ambulatory Recording Venetia) study demonstrated that a persistent high heart rate was an independent predictor of future sustained hypertension, regardless of the initial blood pressure and other confounders (10).

Sympathetic neural factors are involved in energy balance and metabolism as well as in blood pressure control. Therefore, adrenergic overdrive might be implicated in the development and/or progression of the metabolic syndrome

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(11). Sympathetic nerve overactivity is crucial in the pathogenesis of hypertension in type 2 diabetes (12).

The study of Wu et al. (5) focused only on a Chinese population. Other studies have shown that race can have a potential influence on heart rate variability (13). Therefore, further longitudinal studies are needed in other ethnic populations to examine the predictive value of cardiac autonomic function in relation to development of arterial hypertension. Another important point is the gender difference on heart rate variability. There is evidence that women have greater heart rate variability than men, even after controlling for a large number of potential confounders (14).

Normotensive subjects with a family history of hypertension are known to be characterized by altered cardiovascular morphology and reactivity (15). Although the reason for this has not yet been completely clarified, it has been suggested that an imbalance in the autonomic nervous system might play an important role. Pitzalis et al. (16) studied whether autonomic control of heart rate and cardiac structure and function are impaired early in the offspring of hypertensive families. Their main findings were that arterial blood pressure, autonomic control of heart rate, and diastolic function were significantly different in normotensive subjects with a positive family history of hypertension from those without. They speculated that the mechanisms controlling cardiovascular function were already modified in the pre-hypertensive state and that these changes were strictly related to the male gender. These results strongly suggested once more that the role of gender should be taken into account whenever studies of hypertensive offspring are being evaluated.

The future challenge is to investigate whether nonmedical and medical regimens can restore the equilibrium of the cardiac autonomic balance in normotensive subjects with a positive family history of hypertension and in subjects with pre-hypertension in order to prevent or delay the development of hypertension and its cardiovascular damage.

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